AKD-2023: A novel miticide. Biological activity and mode of action

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Abstract: AKD-2023, 3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate (proposed common name acequinocyl) is a novel miticide now under commercial development. It has outstanding miticidal activity against economically important spider mites with the new mode of action of inhibition of mitochondrial electron transfer at complex III.

Keywords: miticide; acequinocyl; AKD-2023; metabolism; complex III; mitochondrial electron transfer

Spider mites on agricultural crops such as food crops, fibre crops and ornamentals are usually phytophagous and cause severe damage in terms of deterioration in product quality and inhibition and retardation of plant growth. They multiply rapidly in sites where insecticides are applied frequently and natural predators of mites are eventually eliminated. It is widely known that their short life cycle tends to favour development of a population of mites resistant to miticides.[1,2] Spider mites have already built up resistance to most of the commercial miticides that have been launched recently on the market.

AKD-2023, 3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate (proposed common name acequinocyl) contains a quinone moiety in its structure that does not occur in the existing commercial miticides and possesses unique miticidal activity. This chemical is now under commercial development. Some physicochemical properties of acequinocyl are given in Table 1. This summary reports its biological efficacy and identifies its target site of action.

A leaf disc study was used to evaluate miticidal activity against two-spotted spider mite (*Tetranychus urticae* Koch), Kanzawa spider mite (*T kanzawai* Kishida), European red mite (*Panonychus ulmi* Koch) and citrus red mite (*P citri* Meg), using a solution of technical grade AKD 2023 in acetone. All the developmental stages, from eggs to adults, of the above mites were affected. This activity is considered to originate primarily as a result of contact action and secondarily as a result of oral uptake, but not from the vapour phase.

A mode of action study, using thoraces of the housefly (*Musca domestica* L), was carried out to identify the site of action on the electron-transfer system in mitochondria. Monitoring oxygen consumption showed that AKD-2023 itself did not inhibit electron transfer but that its de-acetylated metabolite 2-hydroxy-3-dodecyl-1,4-naphthaquinone (DHN) was clearly an inhibitor in that the electron-transfer system inhibited by pyridaben was restored by succinate but again inhibited by DHN. The inhibition by DHN was not restored by succinate but was restored by ascorbate + TMPD. From these results, the activity was suspected to originate from the quinone metabolite DHN produced by hydrolysis of AKD-2023 in mite cells. This DHN inhibited electron transfer at Complex III, thus differing from most of the existing commercial miticides which inhibit at Complex I. The transformation of AKD-2023 into DHN was confirmed by monitoring DHN production when AKD-2023 was incubated with an isolated mitochondrial preparation.[4,5]

Table 1. Physicochemical properties of AKD-2023

Molecular mass	358.52
Melting point	59.6 °C
Log P_{ow}	>6.2
Water solubility	6.7×10^{-6} g litre^{-1} at 25 °C
Chemical Stability	Stable at pH <7.0; unstable at pH >7.0
Photostability	Degradable by light (specifically UV light)

As AKD-2023 possessed the requisite biological efficacy and mode of action, a formulation study was performed to produce a viable commercial product. The technological problems were low melting point and photodegradability, which had to be overcome to obtain a stable product with field efficacy. EC, WP, EW, SC and SL formulations were developed. The activity against Kanzawa spider mite in leaf disc trials was excellent with the EC and SC formulations, but not with the SL and WP. Results from field trials with the EC, SC and EW formulations, carried out at official experiment stations, indicated high activity with the EC and EW for an initial period after application, but activity then decreased sharply. Only with the SC was high activity maintained for longer than one month. Results from formulation and biological activity studies indicated that AKD-2023 was contact-active against the mites, that it was degraded by sunlight when used in a liquid form but that it maintained its activity when used in a particulate form, as was suggested by its physicochemical properties.

Official field trials performed from 1990 to 1996 with an AKD-2023 SC formulation in prefectural experiment stations and universities clearly indicated high activity against two-spotted spider mite, Kanzawa spider mite, European red mite and citrus red mite which lasted for more than one month, and activity even against mites which had been identified as resistant to some of the existing commercial miticides.

AKD-2023 is now under development as the SC

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(*Received 30 July 1998; accepted 16 February 1999*)

formulation Kanemite® in Japan and in some other countries where the problems of resistant mites have become pronounced. It is clear that the quinone metabolite DHN is the active moiety, that it is produced metabolically in mite cells and, because it acts at Complex III stage, that it can be used to control mite populations which are resistant to other miticides.

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Verbena × *hybrida* flower volatiles attractive to Western flower thrips, *Frankliniella occidentalis*

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Abstract: Western flower thrips (WFT) are attracted to three flowering verbena cultivars. The volatile components of these cultivars contain different enantiomers of linalool oxide which have been synthesised and one shown to be attractive to WFT.

Keywords: Western flower thrips; *Frankliniella occidentalis*; *Verbena* × *hybrida*; linalool oxide; enantioselective synthesis

Integrated pest management strategies involving the use of predators are commonly used for control of the Western flower thrips (WFT), *Franklinella occidentalis* Perg, in glasshouses. In agricultural studies, trap crops have shown potential as part of a 'push pull' strategy to concentrate pest insects in particular areas where control agents can be applied. The use of such a strategy under glass would reduce application times and costs of biocontrol agents against pest insects. In glasshouse trials, flowering *Verbena* × *hybrida* Voss plants attracted WFT from ivy geraniums and chrysanthemums and are therefore potential trap plants. Furthermore, the flower volatiles isolated from Sissinghurst Pink, Tapien Pink and Pink Parfait verbena cultivars were particularly attractive to WFT in olfactometer tests. The volatiles identified have potential for increasing the attractiveness of verbena trap plants or attracting thrips to sticky traps at times when verbena plants are not available.

Table 1. Relative proportions of volatile components from air entrainment over flowers of three cultivars of verbena, estimated by GC trace integration as a percentage of the total

Compound	*Sissinghurst Pink (%)*	*Pink Parfait (%)*	*Tapien Pink (%)*
Benzaldehyde	–	–	1.0
Methyl benzoate	–	2.1	–
(*E*)-β-Ocimene	14.4	–	–
(*S*)-Linalool	trace	1.8	11.5
(6*S*)-Pyranone **9**	5.3	5.4	–
(3*E*)-4,8-Dimethyl-1,3,7-nonatriene	5.6	16.7	–
(3*R*,6*S*)-Pyranol **3**	9	1.4	86
(3*S*,6*S*)-Pyranol **5**	7.6	61.3	–
Pentadecane	33.6	–	–
(3*E*,7*E*)-4,8,12-Trimethyl-1,3,7,11-tridecatetraene	1.0	5.1	–

Volatiles from the three cultivars were collected by air entrainment and the major components characterised by GC-MS and GC coinjection with authentic standards (Table 1). The major components of Tapien Pink and Pink Parfait were shown to be different isomers of linalool oxide, both of which were present in Sissinghurst Pink. Elucidation of the structure of the major Tapien Pink and Pink Parfait volatiles was achieved by microcell [^{1}H]NMR spectroscopy, which revealed that the Tapien Pink volatile (400 μg) and the Pink Parfait volatile (40 μg) were diastereoisomers of linalool oxide pyran. Other components identified in both volatiles were an oxidised linalool oxide isomer, a tetraene and a nonatriene, all of which were synthesised for stereochemical assignment. Synthesis of all four enantiomerically pure isomers of the linalool oxide pyrans was performed as shown (Fig 1). The *N*-phenyl carbamate group is electron-withdrawing and so dihydroxylation of **1** with AD-mix β at $<5\,^{\circ}C$ was regioselective for the more reactive alkene. [AD-mix-α and AD-mix-β are asymmetric dehydroxylation reagents (supplied by Aldrich Chemical Co) which are enantioselective.] Protection of the secondary alcohol of **2** by acetylation was followed by cyclisation and deprotection to generate the two diastereoisomers **3** and **4** which were separated by chromatography.[1] The other two enantiomerically pure diastereoisomers of linalool oxide pyran, **5** and **6**, were synthesised in the

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Contract/grant sponsor: Ministry of Agriculture Food and Fisheries
Contract/grant sponsor: Biotechnology and Biological Sciences Research Council
(*Received 3 July 1998; accepted 16 February 1999*)